



## Phenolic compounds from the rhizome of *Renealmia nicolaioides* Loes.: a new diarylheptanoid

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**Abstract:** This study aims to identify phenolic compounds in dichloromethane and methanolic extracts of the rhizome of *Renealmia nicolaioides* collected in the North Region of Brazil. Two known diarylheptanoids, 1,7-bis(4-hydroxyphenyl)-(1E)-1-hepten-3-one (1), and 5R-1,7-bis(4-hydroxyphenyl)-1E-hepten-5-ol (2), and a new one (1R,2S,5S)-2-hydroxy-1,7(p-hydroxyphenyl)-centrolobine (3), as well as one flavonoid, 3-metoxi-quercetin (4) were isolated by chromatographic procedure and identified by spectroscopic techniques (<sup>1</sup>H and <sup>13</sup>C NMR, HRMS and CD). The acetyl derivative of 2 was used to confirm its structure. All four compounds are reported for the first time for this genus, and this is the first occurrence of compound 1 as a natural metabolite. The results reported here are unprecedented for the genus *Renealmia*.

**Key words:** Flavonoid, Alpinieae tribe, Zingiberaceae, underground organ.

### INTRODUCTION

The genus *Renealmia* L.f. belongs to the family Zingiberaceae, subfamily Alpinioideae, and tribe Alpinieae, and contains approximately 75 species distributed throughout tropical regions of the Americas and Africa (Maas 1977). In Brazil, the genus is represented by 21 species distributed throughout several regions and phytogeographical domains of the country including Amazonia,

Caatinga, Cerrado, Atlantic Forest, Pampa, and the Pantanal (Maas and Maas 2015). Some species of *Renealmia* are used for medicinal purposes, with anticancer activity and snakebite treatment being the most notable (Negrelle 2015).

Phytochemical investigations have been conducted with species of *Renealmia* and have revealed the presence of terpenes, flavonoids and diarylheptanoids (Luz et al. 1984, Ramiandrasoa et al. 1986, Lognay et al. 1991, Zhou et al. 1997, Yang et al. 1999, Kaplan et al. 2000, Sekiguchi et al. 2001, 2002, Gu et al. 2002, Maia et al. 2007,

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Cabanillas et al. 2014, Gilli et al. 2014, Gómez-Betancur et al. 2014, 2015, Noriega et al. 2016).

Flavonoids isolated from roots of *R. nicolaioides* induced quinone reductase enzyme phase II, which acts in the protective mechanism against tumor action in hepatocytes (Gu et al. 2002). Flavonoids and diarylheptanoids isolated from the ethanolic extract of *R. thyrsoides* rhizome acted against the amastigote form of *Leishmania amazonensis* (Cabanillas et al. 2014). Pinostronbin, a flavanone isolated from leaves of *R. alpinia*, inhibited enzymatic and biological activities of PLA2, which is the most abundant and important constituent of snake venoms (Gómez-Betancur et al. 2016).

Most diarylheptanoids are phenols whose anti-cancer activity has been widely investigated (Wei et al. 2005, Dong et al. 2015, Agrawal et al. 2010, Cabanillas et al. 2014, Gilli et al. 2014).

Among the compounds isolated from *Renalmia* spp., phenols stand out. Thus, this work aims to identify the phenolic compounds present in the rhizome of *R. nicolaioides*.

## MATERIALS AND METHODS

### PLANT MATERIAL

Rhizomes of *R. nicolaioides* were collected in June 2015, at the Catuaba Experimental Farm and the Humaitá Forest Reserve, both located in Rio Branco, state of Acre. The material was identified and a voucher (No. 6646) was deposited in the herbarium of the Universidade Federal do Acre (UFACPZ).

### EQUIPMENT

One- and two-dimensional  $^1\text{H}$  and  $^{13}\text{C}$  nuclear magnetic resonance (NMR) spectra were obtained using a Bruker NMR spectrometer [400 and 500 MHz ( $^1\text{H}$ ), 100 and 125 MHz ( $^{13}\text{C}$ )], using tetramethylsilane (TMS) as internal standard for chemical shift reference. High-resolution

electrospray ionization mass spectrometry (EI-HRMS) using a quadrupole-time-of-flight mass spectrometer (XEVO-QToF) was used to obtain the mass spectra. High-performance liquid chromatography (HPLC) measurements were performed using an instrument equipped with a LC-10AS pump, a SPD-10A detector, a CBM-20A-Communications Module (Shimadzu), and a Rheodyne injector with loop of 500  $\mu\text{L}$ . Optical rotation was performed using a JASCO PTC 203 digital polarimeter and a JASCO J-815 CD spectrometer.

### EXTRACTION AND ISOLATION

Air-dried powdered rhizomes (155 g) were successively extracted with  $\text{CH}_2\text{Cl}_2$  and  $\text{CH}_3\text{OH}$  at room temperature. Three extractions were made with dichloromethane, while the extraction with the methanol was exhaustive. The periodicity of solvent exchange was on average 48 hours, and each solution was concentrated on a rotary evaporator under vacuum. This process yielded two extracts: dichloromethane rhizome (RNRD) and methanol rhizome (RNRM).

The RNRD extract (1.05 g) was subjected to silica gel column chromatography (CC) eluted with solvents of increasing polarity [n-hexane:dichloromethane (1:1 to 2:8) and chloroform:methanol (1:0 to 9:2)] to give 20 fractions. Fraction 12 (0.14 g) was subjected to silica gel column chromatography (CC) eluted with solvents of increasing polarity [dichloromethane:ethyl acetate (1:0 to 0:1) and methanol] to give eight subfractions. Compound **1** was purified and identified in subfraction 3 (13 mg). Fraction 17 (80 mg) was subjected to column chromatography using Sephadex LH-20 eluted with methanol to give subfractions. The subfraction 17.2 (18 mg) was subjected to fractionation by HPLC. The chromatographic conditions were water:acetic acid (99:1) as solvent (A) and acetonitrile as solvent

(B) in a ratio of 4:6. The mobile phase was filtered before use and delivered isocratically at a flow rate of 1 ml min<sup>-1</sup>. The analysis was conducted at room temperature using a Betasil C18 semi-preparative column (25 mm x 4.6 mm i.d., 5 µm), and the analyses were monitored at 270 nm. In addition to some unidentified components, diarylheptanoid, represented by peak at 5.094 min, was isolated and identified as compound **3**.

The RNRM extract (10 g) was solubilized in methanol:water (3:1) and subjected to liquid-liquid partitioning by organic solvents of increasing polarity [hexano (RNRM-H), dichloromethane (RNRM-D), ethyl acetate (RNRM-Ac), butanol (RNRM-B), and water (RNRM-H<sub>2</sub>O)]. Three-column chromatography (CC) was performed with the dichloromethane fraction.

First, RNRM-D (2 g) was subjected to silica gel column chromatography (CC) eluted with dichloromethane:methanol (1:0 to 0:1) to give 8 fractions. The subfractions 2 (38 mg) and 3 (55 mg) were subjected to column chromatography using Sephadex LH-20 eluted with methanol to give four and six subfractions, respectively. Subfraction 2.4 (86 mg) was subjected to preparative plate chromatography and eluted with chloroform:methanol (9:1) to give two subfractions (2.4.1 and 2.4.2). Compounds **1** and **2** were purified and identified in subfraction 2.4.1 (7 mg) and 2.4.2 (5 mg), respectively. Subfraction 3.1 (48 mg) was subjected to preparative plate chromatography and eluted with chloroform:methanol (9:1) to give two subfractions (3.1.1 and 3.1.2). Compounds **2** and **1** were again purified and identified in subfraction 3.4.1 (21 mg) and 3.4.2 (20 mg), respectively. Fraction 4 (98 mg) was subjected to silica gel column chromatography (CC) eluted with methanol to give three subfractions. The compound **2** was again purified and identified in subfraction 4.1 (36 mg).

Second, RNRM-D (1.7 g) was subjected to a silica gel column chromatography (CC) eluted with chloroform:ethyl acetate (9:1 to 0:1) and

ethyl acetate:methanol (98:2 to 0:1) to give 13 fractions. Compound **1** was again purified and identified in fraction 5. Fraction 8 (0.13 g) was rechromatographed over Sephadex LH-20 eluted with MeOH to give four subfractions. Subfraction 8.2 (0.2 g) was rechromatographed over Sephadex LH-20 eluted with methanol to give four subfractions. Compound **2** was again purified and identified in subfraction 8.2.3 (0.12 g).

Third, RNRM-D (0.6 g) was subjected to column chromatography using Sephadex LH-20 eluted with methanol:dichloromethane (8:2). Compound **4** was purified and identified in fraction 4 (6 mg).

Derivative **2a**. 5*R*-1,7-bis(*p*-acetoxyphenyl)-(1*E*)-1-hepten-5-acetate. This derivative was obtained as described by Bandeira et al. (2007). <sup>1</sup>H and <sup>13</sup>C NMR data of **2a** (400/100 MHz, Methanol-d<sub>4</sub>): 7.38 (d, 8.2 Hz, H-2',6'), 7.02 (d, 8.2 Hz, H-3',5'), 7.23 (d, 8.2 Hz, H-2'',6''), 6.97 (d, 8.2 Hz, H-3'',5''), 6.38 (d, 16.0 Hz, H-1), 6.23 (dt, 16.0 and 7.2 Hz, H-2), 4.98 (qui, 6.8 Hz, H-5), 2.73 and 2.62 (m, H-7), 2.24 (m, H-3), 1.93 (m, H-6), 1.77 (m, H-4); 2.02 (s, 3H, O<sub>2</sub>CCH<sub>3</sub>), and 2.26 (s, 3H) and 2.28 (s, 3H) of 2xO<sub>2</sub>CCH<sub>3</sub>. δ<sub>C</sub>: 171.5, 169.9, 169.8 (3x O-CO-CH<sub>3</sub>), 149.7, 149.0 (C-4'',4''), 139.1 (C-1''), 135.1 (C-1'), 128.9 (C-2',6'), 126.4 (C-2'',6''), 121.3 and 121.2 (C-3',5' e 3'',5''), 73.2 (C-5), 35.5 (C-6), 33.4 (C-4), 30.7 (C-7), 28.6 (C-3). 19.7, 19.5, 19.5 (3x O<sub>2</sub>C-CH<sub>3</sub>). [α]<sub>D</sub> +11.771.

1*R*,2*S*,5*S*-2-hydroxy-1,7(*p*-hydroxyphenyl)-centrolobine (**3**). MP: 160-162° C. UV: λ<sub>max</sub> MeOH, nm (log ε): 285 (0.3), 225 (1.6), 202 (1.5), CD (c 196.25 x 10<sup>-4</sup> mg/mL, MeOH): λ<sub>max</sub> nm (θ mdeg): 275 (0), 225 (+15), 202 (+16), 200 (0); <sup>1</sup>H and <sup>13</sup>C NMR data see Table I. ESI-HRMS: *m/z* (%): positive mode: 315.1599 [M+H, (25)], calc 315.1596, 297.1500 (40), 279.1397 (20), 147.0788 (20), 133.1063 (100), and negative mode: 313.1447[M-H, (100)], calc. 313.1439, 205.0852 (30).

## RESULTS AND DISCUSSION

Three diarylheptanoids were identified, including two known compounds (**1**, **2**) and one new one (**3**), by analysis of 1D and 2D NMR spectra (Figure 1). Compound **1** was identified by two pairs of doublets (8.0 Hz, 2H each) at  $\delta_{\text{H}}$  7.50/6.82, and 7.0/6.69 of two p-substituted aromatic rings, two doublets (15Hz, 1H each) at  $\delta_{\text{H}}$  7.56/6.65 of a *trans*-enone, two triplets (7.5 Hz, 2H each) at  $\delta_{\text{H}}$  2.71 and 2.57, and a multiplet at 1.86 (4H). Analysis of the HMQC spectrum allowed the identification of signals of  $^1J_{\text{HC}}$  of these respective detected protons with carbons at  $\delta_{\text{CH}}$  130.2/115(CH-2',6'/3'.5'), 128.9/114.6 (CH-2'',6''/3'',5''), confirming the two AA'BB' systems, and 143.8/122.3 (CH-1/2) of enone), and  $\delta_{\text{CH}_2}$  39.7, 34.4, 31.1 and 23.9 of CH<sub>2</sub>-4, 7, 5 and 6, respectively. The signals of  $\delta_{\text{C}}$  at 202.2, 160.7, 154.9, 132.9, and 125.6 confirmed the two aromatic rings and the enone in the proposed structure of the diarylheptanoid. These data were compared with those of the synthetic product registered in the literature (Jirásek et al. 2014) and was identified as E-1,7-bis(4-hydroxyphenyl)-hept-1-en-3-one (**1**), identified for the first time as natural product. The same analysis was performed for **2**. In addition to two AA'BB' of aromatic systems [ $\delta_{\text{H}}/\delta_{\text{C}}$ : 7.15/126.8(CH-2'',6''), 6.72/114.5(CH-3'',5''); 7.0/128.8 (CH-2',6'), 6.7/114.6 (CH-3',5'), a *trans* double bond [ $\delta_{\text{H}}/\delta_{\text{C}}$ : 6.30(d, 16 Hz)/129.6 (CH-1), 6.0(dt,  $J_1$  16.0 and  $J_2$  6.8 Hz)/127.0(CH-2)], and one CH [3.59(qui, 7.5 Hz)/70.0(CH)] which  $^{2,3}J_{\text{HC}}$  (HMBC) located at C-5, were confirmed. The heptanoid was completed by for methylene groups with [ $\delta_{\text{H}}/\delta_{\text{C}}$ : 2.25 and 2.30 (m)/28.8 (CH<sub>2</sub>-3), 1.6(m)/36.9 (CH<sub>2</sub>-4), 1.70(m)/39.2(CH<sub>2</sub>-6), 2.55 and 2.70(m)/30.7(CH<sub>2</sub>-7)]. Additional analysis of DEPTQ and HMBC spectra was used to confirm the chemical shift of quaternary carbons of **2**. The new triacetyl derivative (**2a**) was prepared to confirm its structure (see Materials and Methods). These data of the natural diarylheptanoid, including the  $[\alpha]_{\text{D}}$

+20.325, [Lit  $[\alpha]_{\text{D}}$  +3.5( $[\alpha]_{\text{D}}$  0.1, MeOH)], were similar to those of 5*R*-1,7-bis(5-hydroxyphenyl)-(1*E*)-1-hepten-5-ol, isolated from the rhizomes of *Curcuma kwangsiensis* (Li et al. 2010), defining this structure for **2** (Figure 1).

The analysis of  $^1\text{H}$  and  $^{13}\text{C}$  spectra of compound **3** allowed the identification of two aromatic systems similar to compounds **1** and **2**. These spectra, including the 2D experiments ( $^1\text{Hx}^1\text{H}$ -COSY, HMQC and HMBC), showed signals for four methylene groups, and three methyne oxygenated carbons (Table I). The values of *m/z* detected by HRMS in negative mode, *m/z* 313.1442, and in positive mode, *m/z* 315.1599, were used to confirm the proposed structure as **3** (Figure 1). The  $\delta_{\text{C}}$  and  $\delta_{\text{H}}$  detected in the HMQC spectrum, the multiplicity allied to  $J_{\text{H,H}}$  values, as well as analyses of  $^1\text{Hx}^1\text{H}$ -COSY and HMBC spectra in methanol and in  $\text{CDCl}_3$ , such as the  $^3J_{\text{HC}}$  of H-7/C-5, H-1/C-2, and H-1/H-5 (Table I), lead to the proposal of a pyran ring as shown in **3** (Figure 1). The relative stereochemistry was based on the NOE signals observed in the NOESY experiments, such as H-1/H-3, H-1/H-5, and by  $J_{\text{H,H}}$  value (9.0 Hz) of H-1<sub>ax</sub>/H-2<sub>ax</sub>. Positive EC observed in the dichroism circular spectrum ( $\Theta$ : 15 mdeg,  $\lambda_{\text{max}}$  225 nm, methanol), is compatible with an R configuration of oxybenzyl carbon, such as the observed positive EC for C-2 (oxybenzyl) of flavonoid (Slade et al. 2005). These data, allied with relative stereochemistry, allowed the definition of the absolute stereochemistry of this new compound (**3**) as 1*R*,2*S*,5*S*-2-hydroxy-1,7(*p*-hydroxyphenyl)-centrolobine (**3**) (Figure 1).

Compound **4** was identified as flavonoid by  $^1\text{H}$ ,  $^{13}\text{C}$  (MeOH-*d*<sub>4</sub>, 500/125 MHz) 1D and 2D spectral analyses and comparison with literature data. Signals at  $\delta_{\text{H}}$  6.2(bs), 6.4(bs), 6.91 (d, 8.0Hz), 7.53(bd, 8.0 Hz) and 7.63(bs) of protons linked to carbons at  $\delta_{\text{CH}}$  99.8, 94.7, 116.0, 116.4, 122.3 of CH 6, 8, 5', 6' and 2', respectively. An additional singlet at  $\delta_{\text{CH}_3}$  3.79 of 3H with  $^1J_{\text{HC}}$  and  $^3J_{\text{HC}}$  with carbons at  $\delta_{\text{CH}_3}$  59.1



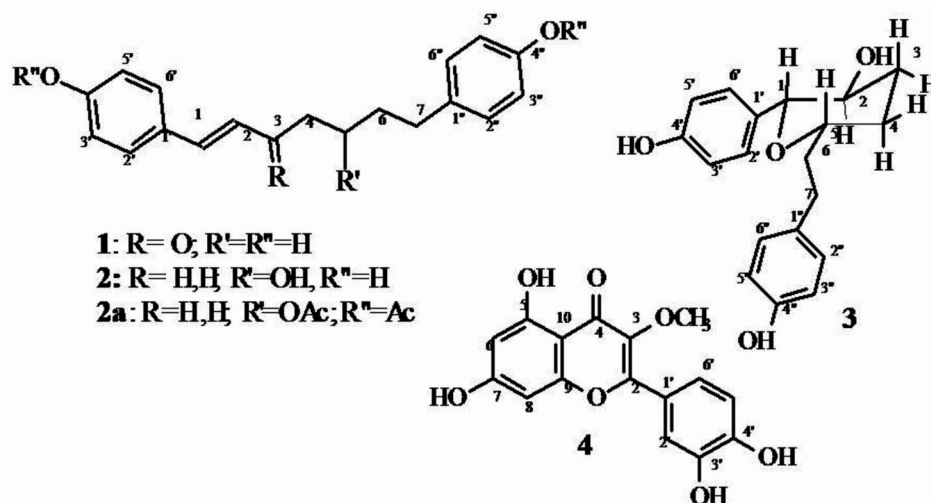


Figure 1 - Structures of compounds isolated from rhizomes of *R. nicolaioides*.

and  $\delta_c$  138.0, respectively, allowed the inclusion of a methyl group at C-3 in the flavonoid structure. The additional signals of  $\delta_c$  detected in the DEPTQ NMR spectrum, and the value of  $m/z$  316 ( $M^+$ ) observed in the mass spectrum, were compatible with the quercetin 3-methyl ether. These data are similar to those of the flavonoid registered in the literature (Rashed et al. 2014).

Compound **1**, which is a bisdemethoxycurcumin derivative, is being described for the first time from a natural source, although it had been previously synthesized (Jirásek et al. 2014).

Diarylheptanoid **2** has been detected in rhizomes of *Curcuma* species (Zingiberaceae) *C. comosa* Roxb., *C. elata* Roxb. and *C. kwangsiensis* S.K. Lee & C.F. Liang. This compound has been shown to exhibit antiallergic activity, potent cytotoxic activity against both the KB and NCI-H187 cell lines, and inhibitory activity for melanogenesis, and may be used in the treatment of skin diseases (Li et al. 2010, Matsumoto et al. 2013, 2015, Chokchaisiri et al. 2014).

Flavonoid **4** was isolated from the rhizome of *R. nicolaioides*. Other flavonoids have also been isolated from the roots of *R. nicolaioides* (Gu et al. 2002), the leaves of *R. thyrsoidea*, *R. cernua* and *R. alpinia* (Cabanillas et al. 2014, Gilli et al. 2014,

Gómez-Betancur et al. 2014, 2015), and from the rhizome of *R. thyrsoidea* (Cabanillas et al. 2014). Flavonoids are used as chemosystematic markers for the Zingiberaceae (Lima and Kaplan 2010), and are commonly found among its genera.

The occurrence of the diarylheptanoids **1** and **2** in four different fractions from the rhizome of *R. nicolaioides* could be potential chemotaxonomic markers for this species. Further phytochemical studies with other species of *Renealmia* are needed to fully understand the chemosystematic significance of these compounds for this genus. Compound **3** can be considered as a biosynthetic precursor of **2**.

The high diversity of metabolites found in the Amazonian *Renealmia nicolaioides* strongly recommends further investigation into the chemical and biological properties of the species.

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**TABLE I**  
<sup>1</sup>H and <sup>13</sup>C NMR data of diarylheptanoid 3 in D<sub>3</sub>CO-D (500MHz) and CDCl<sub>3</sub> (600 MHz).

C	δ <sub>H</sub>	δ <sub>C</sub>	δ <sub>H</sub>	δ <sub>C</sub>	<sup>2,3</sup> J <sub>HC*</sub>	NOE*
	D <sub>3</sub> CO-D		CDCl <sub>3</sub>			
1	3.98 (d, 9Hz)	84.3	3.98 (d, 9.0 Hz)	86.3	C-1', 2; 3; 5;2',6'	H-2',6'; 5;3
2	3.48(m)	70.0	3.5 (td, 9.0, 9.0, 4.2 Hz)	71.9		2'.6'; 3eq; 4ax;
3	2.1(m);1.55(m)	33.9	2.12(dbr, 12 Hz); 1.55 (m)	34.3		H-1; 4
4	1.50(m), 1.75(m)	31.4	1.77(m); 1.49(m)	32.5		H-7
5	3.48(m)	76.6	3.40(m)	78.4		H-6; 7
6	1.66; 1.74(m)	38.1	1.75(m), 1.60(m)	39.0	C-1'';5;7	H-2'',6''; 7
7	2.7 m (2H)	31.0	2.57(m)	32.0	C-1''; 2'',6'';6;5	H-2'',6''; 4; 1
1'	-	132.3	-	132.9		-
2',6'	7.34 (d, 8Hz)	129.4	7.12(d, 9.0Hz)	130.3	C-1;4';	H-1;5
3',5'	6.84 (d, 8Hz)	114.9	6.77(d, 9.0 Hz)	116.0	C-4';2',6';1'	
4'	-	157.0	-	158.4		
1''	-	132.7	-	134.5		
2'',6''	7.15 (d, 8Hz)	129.6	6.97(9.0Hz)	130.4	C-7;4'';1''	H-7; 6;4
3'',5''	6.80 (d, 8Hz)	115.3	6.66(9.0)	116.0	C-4'';1''	
4''	-	155.7	-	156.3		

\*From the observed signs with two solvents.

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#### AUTHOR CONTRIBUTIONS

KVG and HRPL participated in sample collection and identified the species. KVG, MGC, IGS and RNC performed the chemical analyzes. KVG, MGC, HRPL and MDC analyzed the data and wrote the paper.

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